SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name:	Sodium hyaluronate
Device Trade Name:	ORTHOVISC® High Molecular Weight Hyaluronan
Applicant's Name and Address:	Anika Therapeutics, Inc. 160 New Boston Street Woburn, MA 01801
Premarket Approval (PMA) Application Number:	P030019
Date of Panel Recommendation:	None
Date of Notice of Approval to the Applicant:	February 4, 2004

II. INDICATIONS FOR USE

ORTHOVISC® is indicated in the treatment of pain in osteoarthritis (OA) of the knee in patients who have failed to respond adequately to conservative non-pharmacologic therapy and to simple analgesics (e.g., acetaminophen).

III. CONTRAINDICATIONS

- Do not administer to patients with known hypersensitivity (allergy) to hyaluronate preparations.
- Do not administer to patients with known allergies to avian or avian-derived products (including eggs, feathers, or poultry).
- Do not inject ORTHOVISC® in the knees of patients with infections or skin diseases in the area of the injection site or joint.

IV. WARNINGS AND PRECAUTIONS

Refer to product labeling.

V. DEVICE DESCRIPTION

ORTHOVISC® High Molecular Weight Hyaluronan is a sterile, non-pyrogenic, clear viscoelastic solution consisting of sodium hyaluronate in physiologic saline and contained in a single-use syringe. The hyaluronic acid of ORTHOVISC® is extracted from rooster combs. Sodium hyaluronate is a natural complex sugar of the glycosaminoglycan family. The sodium hyaluronate polymer consists of repeating disaccharide units of sodium glucuronate-N-acetylglucosamine. The molecular weight range of hyaluronic acid in ORTHOVISC® is between 1 and 2.9 million daltons. ORTHOVISC® has a nominal sodium hyaluronate concentration of 15 mg/mL, dissolved in physiologic saline that contains 9 mg/mL sodium chloride and USP sterile water for injection. It is supplied in a 3.0 mL glass syringe containing 2.0 mL of ORTHOVISC®. The contents of the syringe are sterile and non-pyrogenic.

Each pre-filled syringe with 2 mL of ORTHOVISC® contains:

Sodium hyaluronate	30 mg
Sodium chloride	18 mg
USP water for injection	q.s. to 2 mL

VI. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

- Infection
- Arthralgia (knee pain)
- Arthrosis
- Joint (knee) disorder
- Joint (knee) swelling
- Joint (knee) effusion
- Joint (knee) stiffness
- Pain in limb
- Tendonitis
- Paraesthesia
- Phlebitis
- Pruritus
- Injection site erythema
- Injection site edema
- Injection site pain
- Injection site reaction
- Arthropathy
- Baker's cyst
- Bursitis
- Localized osteoarthritis
- Aggravated osteoarthritis
- Immune Response

VII. ALTERNATIVE PRACTICES AND PROCEDURES

For patients who have failed to respond adequately to conservative non-pharmacological therapy and simple analgesics (e.g., acetaminophen), alternative practices and procedures include nonsteroidal anti-inflammatory drugs (NSAIDs); intra-articular injection of corticosteroid; avoidance of activities that cause joint pain; exercise; physical therapy; and removal of excess fluid from the knee. For patients who have failed the above treatments, surgical interventions such as arthroscopic surgery and total knee replacement are also alternative treatments.

VIII. MARKETING HISTORY

Anika Therapeutics has marketed ORTHOVISC® in the European Union and other European countries recognizing the CE Mark since September 1996. ORTHOVISC® is also currently marketed in Canada, Turkey, Egypt and Israel. ORTHOVISC® has not been withdrawn from marketing for any reason related to safety and effectiveness of the device.

IX. SUMMARY OF PRECLINICAL STUDIES

Preclinical studies were conducted to evaluate the safety and performance characteristics of ORTHOVISC®, High Molecular Weight Hyaluronan including microbiological studies, biological and safety evaluations.

Microbiological Studies

A validation study of Poliovirus (PV1) and SV-40 removal/inactivation from rooster combs was performed to evaluate the removal or inactivation of these two viruses during the purification process used to extract hyaluronic acid (HA) from rooster combs. The validation study showed that PV1 and SV-40 were effectively removed during the first two steps of the purification process. The product did not contain detectable infectious viruses at the end of either of the spiked processes.

Biological Evaluation

ORTHOVISC® High Molecular Weight Hyaluronan was tested for biocompatibility in accordance with the requirements of ISO 10993-1, Biological Evaluation of Medical Devices. ORTHOVISC® was considered to be biocompatible under the conditions of the studies performed. Each of the tests is briefly summarized below.

- Intracutaneous Toxicity (USP) Study - Under the conditions of the study, there was evidence of apparent irritation from ORTHOVISC® injected intracutaneously into rabbits. Slight to moderate edema was observed throughout the study. Histopathology strongly suggested that the moderate irritation observed was due to tissue fluid accumulation associated with the test article rather than true edema. No evidence of histomorphologic alterations of the blood vessels nor cellular alterations indicative of local irritation was observed.

- Systemic Toxicity (USP) Study - Under the conditions of the study, there was no mortality or evidence of significant systemic toxicity from ORTHOVISC® injected systemically into mice.

- Sister Chromatid Exchange Assay - Under the conditions of the assay, the ORTHOVISC® solution was not considered mutagenic to Chinese Hamster Ovary cells.

- Chromosomal Aberration Assay - Under the conditions of the assay, the ORTHOVISC® solution was not considered mutagenic to Chinese Hamster Ovary cells.

- Ames Salmonella/Mammalian Microsome Mutagenicity Assay - Under the conditions of the assay, the ORTHOVISC® solution was not considered mutagenic to Salmonella typhimurium tester strains.

- Delayed Contact Sensitization Study Using a Maximization Method - Under the conditions of the test, ORTHOVISC® showed no evidence of causing delayed dermal contact sensitization in the guinea pig.

- Cytotoxicity Test Using the Agarose Overlay Method - Under the conditions of the test, ORTHOVISC® showed no evidence of causing cell lysis or toxicity.

- USP 7 Day Muscle Implantation Study - Under the conditions of the test, the macroscopic reaction of ORTHOVISC® was not significant as compared to the USP negative control implant material.

- USP 30 Day Muscle Implantation Study with Histopathology - Under the conditions of the test, the macroscopic reaction of ORTHOVISC® was not significant as compared to the USP negative control implant material. Microscopically, ORTHOVISC® was classified as a non-irritant as compared to the USP negative control material.

- In Vitro Hemolysis Test (Direct Contact) - Under the conditions of the test, the solution of ORTHOVISC® in saline was not considered to be hemolytic.

X. SUMMARY OF CLINICAL STUDIES

The safety and effectiveness of ORTHOVISC® for the treatment of osteoarthritis of the knee were evaluated in three randomized, controlled, double-blind multicenter studies performed in the U.S and Canada. Two of the randomized studies (OAK9501 and OAK2001) utilized unilateral treatment and form the basis of safety and effectiveness for the PMA approval of ORTHOVISC®. The other randomized study (OAK9801) utilized bilateral treatment. Because bilateral treatment confounded the assessment of effectiveness of the OAK9801 Study, this data was not included in the effectiveness assessment, but it is used for the safety analysis.

A. Study Design

The objective of the studies was to assess the safety and effectiveness of ORTHOVISC® for the treatment of joint pain patients with idiopathic osteoarthritis of the knee. The OAK9501 study randomized patients to 3 weekly injections of either ORTHOVISC® (O3) or saline (Saline). The OAK2001 study randomized patients to one of three treatments: 4 ORTHOVISC® injections (O4), 3 ORTHOVISC® injections + 1 arthrocentesis procedure (O3A1), or 4 arthrocentesis procedures (A4).

Inclusion/Exclusion Criteria

Important inclusion criteria were:

- Baseline WOMAC Pain Score (sum of five 100-mm components) in the index knee ≥200 mm (OAK9501) or 200-400 mm (OAK2001)
- Contralateral knee WOMAC Pain Score <200 mm (OAK9501) or <150 mm (OAK2001)
- Wash-out of all NSAIDs, corticosteroids and other analgesics prior to study initiation
- Age range >50 years (OAK9501) or 40-75 years (OAK2001)
- Index knee Kellgren-Lawrence (K-L) grade II or III (OAK9501) or I-III (OAK2001)

Exclusion Criteria included:

- Infection in the joint or surrounding skin
- Intra-articular neoplasm
- Inflammatory joint disease, OA in the hips, osteonecrosis, moderate to marked effusion from index knee
- Positive synovial fluid culture
- Reduced range of motion
- Large knee circumference (>45 cm)
- Recent intra-articular HA
- Immuno-suppressives, anti-coagulants, NSAIDs, anti-depressants, anti-convulsants
- Recent knee trauma or surgery
- Bursitis
- Full-thickness cartilage loss in index knee
- Fibromyalgia
- Vascular insufficiency and hemiparesis

B. Patient Population and Demographics

OAK9501 included 385 patients at 21 centers, and OAK2001 involved 373 patients at 24 centers, both in the U.S. and Canada. Within the individual studies, baseline and demographic variables were similar among groups. Table 1 below summarizes the baseline and patient demographic characteristics for the combined effectiveness subgroup.

Table 1: Baseline and patient demographics summary—effectiveness subgroup.*

Variable	O3 N=83 N (%)/Mean±SD	Saline N=81 N (%)/Mean±SD	O4 N=104 N (%)/Mean±SD	O3A1 N=90 N (%)/Mean±SD	A4 N=100 N (%)/Mean±SD
Gender (% male)	32 (38.6)	32 (39.5)	58 (55.8)	45 (50.0)	50 (50.0)
Age (years)	64.6±8.2	67.7±8.5	58.6±8.9	59.2±8.6	59.0±8.1
BMI (kg/m^2)	32.0±6.5	29.7±6.2	29.0±4.2	29.9±4.3	29.6±3.9
Radiographic Evaluation:					
K-L Grade II	37 (44.6)	32 (39.5)	56 (53.8)	58 (64.4)	53 (53.0)
K-L Grade III	46 (55.4)	49 (60.5)	48 (46.2)	32 (35.6)	47 (47.0)
WOMAC Pain Score - index knee (mm)	274.1±64.9	268.2±69.3	288.2±59.8	289.7±49.5	293.4±58.7
WOMAC Pain Score - contralateral knee (mm)	83.1±57.0	87.0±54.2	68.7±47.1	69.7±47.0	67.8±48.3
Pain on Standing Score (mm)	51.2±24.7	46.9±23.2	64.8±18.4	65.4±16.9	65.9±15.8
Investigator Global Score (mm)	53.3±19.0	50.6±19.4	58.8±14.3	58.2±14.3	57.8±14.7
Patient Global Score (mm)	55.7±20.4	53.4±21.6	67.3±14.9	62.4±16.5	64.3±14.9

* Patients from OAK2001 & OAK9501 with Kellgren-Lawrence radiographic grades of II or III at baseline and WOMAC pain in the contralateral knee of <175mm (out of 500).

O3 3 weekly ORTHOVISC® injections – OAK9501 Study
Saline 3 weekly control [saline injection] procedures – OAK9501 Study
O4 4 weekly ORTHOVISC® injections – OAK2001 Study
O3A1 3 weekly ORTHOVISC® injections + 1 control [arthrocentesis only] procedure – OAK2001 Study
A4 4 weekly control [arthrocentesis only] procedures – OAK2001 Study

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C. Treatment and Evaluation Schedule

After screening, a baseline assessment (including baseline pain scores) was made. Immediately following baseline assessment, the first injection was given, followed by weekly injections for 2 (OAK9501) or 3 (OAK2001) additional weeks. Follow-up then occurred at weeks 7/8, 11/12, 15/16 and 21/22. Final follow-up was at week 27/28. Patients were permitted "rescue" acetaminophen (up to 4 g per day), which was monitored at follow-up visits.

D. Safety Results

A total of 981 patients were enrolled in three multicenter, double-blind, randomized controlled clinical studies. All medical events that occurred during the entire study period of each trial (27/28 weeks), regardless of relationship to study procedures, were considered adverse events. A safety analysis was performed, using summary data on adverse events from these three clinical studies. The population consisted of 562 ORTHOVISC® patients (434 receiving 3 injections and 128 receiving 4 injections), 296 patients who received 3 saline injections as the control treatment and 123 patients who received 4 arthrocentesis procedures as the control treatment.

Adverse events, device related or not, occurred in 62% of ORTHOVISC® patients, 69% of Saline patients and 53% of Arthrocentesis patients. Adverse events occurring at a rate of >5% in the overall population included: arthralgia (which occurred in 12.6% of ORTHOVISC® patients, 17.2% of Saline patients and 0.8% of Arthrocentesis patients), back pain (which occurred in 6.9% of ORTHOVISC® patients, 12.2% of Saline patients and 4.9% of Arthrocentesis patients) and headache not other wise specified (NOS) (which occurred in 12.1% of ORTHOVISC® patients, 16.6% of Saline patients and 17.9% of Arthrocentesis patients). Generally, the rates of individual adverse effects were similar among the three groups. Injection site pain occurred in 2.5% of ORTHOVISC® patients, 2.0% in the saline patients, and 0.8% in the arthrocentesis patients. Table 2 lists local individual adverse events reported on a by-patient basis for the combined intent-to-treat (ITT) populations of the three studies.

Table 2: Local individual adverse events reported on a by-patient basis for the combined ITT populations of the three studies.

Adverse Event	ORTHOVISC N = 562	Saline N = 296	Arthrocentesis N = 123
Any Adverse Event	349 (62.1%)	204 (68.9%)	65 (52.8%)
Injection site erythema	2 (0.4%)	0 (0%)	0 (0%)
Injection site edema	5 (0.9%)	1 (0.3%)	0 (0%)
Injection site pain	14 (2.5%)	6 (2.0%)	1 (0.8%)
Injection site reaction NOS[1]	1 (0.2%)	2 (0.7%)	1 (0.8%)

Pain NOS[1]	14	(2.5%)	11	(3.7%)	1	(0.8%)
Arthralgia	71	(12.6%)	51	(17.2%)	1	(0.8%)
Arthritis NOS[1]	4	(0.7%)	5	(1.7%)	0	(0%)
Arthropathy NOS[1]	5	(0.9%)	3	(1.0%)	0	(0%)
Baker's cyst	2	(0.4%)	2	(0.7%)	0	(0%)
Bursitis	6	(1.1%)	6	(2.0%)	2	(1.6%)
Joint disorder NOS[1]	2	(0.4%)	0	(0%)	0	(0%)
Joint effusion	2	(0.4%)	1	(0.3%)	1	(0.8%)
Joint stiffness	3	(0.5%)	2	(0.7%)	0	(0%)
Joint swelling	4	(0.7%)	2	(0.7%)	1	(0.8%)
Localized osteoarthritis	5	(0.9%)	1	(0.3%)	1	(0.8%)
Aggravated osteoarthritis	2	(0.4%)	0	(0%)	1	(0.8%)
Knee arthroplasty	3	(0.5%)	2	(0.7%)	0	(0%)

Notes: [1]NOS = Not otherwise specified.

E. Effectiveness Results:

When each study was analyzed individually, the primary analyses for each study did not show statistical significance. An additional effectiveness analysis using combined data from these two studies was performed. The combined data consisted of data obtained from a subgroup of patients from each of the studies (the "ITT Subgroup" from OAK9501 and the "Evaluable Subgroup" from OAK2001) who had Kellgren-Lawrence radiographic grades of II or III at baseline and Western Ontario and McMaster Universities Arthritis Index (WOMAC) pain in the contralateral knee of <175mm (out of 500) and is referred to as the effectiveness subgroup population. Contralateral knee pain was believed to confound the results of the OAK9501 Study and inclusion of patients with Kellgren-Lawrence radiographic grade I in the OAK2001 Study was believed to confound the results of that study. The revised criteria for Kellgren-Lawrence score and contralateral knee pain in the effectiveness subgroup population addresses these confounding variables.

For the effectiveness subgroup population. the primary effectiveness analysis performed was to determine the proportion of patients achieving a 20%, 40%, and 50% improvement from baseline in WOMAC Pain Score in conjunction with a minimum absolute improvement of 50 mm from baseline in the WOMAC Pain Score at four assessment point between Weeks 7/8 to 21/22 for the index knee.

Assessment of treatment effectiveness was as follows:

- OAK9501: Four primary endpoints, assessed using the 5-point Likert scale – Patient Global Score, Investigator Global Score, Pain on Standing Score and Pain after Walking 50 Feet Score; secondary endpoints included WOMAC Pain Score, WOMAC Stiffness Score, WOMAC Function Score and Time to Walk 50 Feet.

- OAK2001: One primary endpoint – proportion of patients achieving 20% improvement (and at least 50 mm absolute improvement) from baseline in WOMAC Pain Score over weeks 8-22, based on the 500-point scale; four secondary endpoints – mean changes from baseline in the WOMAC Pain Score, Pain on Standing Score, Investigator Global Score and Patient Global Score. If there were no statistically significant differences achieved between the active and control groups for the primary endpoint there was a prospectively defined plan to increase the individual patient success to ≥ 40% improvement and to ≥ 50% improvement.

- Combined Study Population: For the effectiveness subgroup population the primary effectiveness analysis performed was to determine the proportion of patients achieving a 20%, 40%, and 50% improvement from baseline in WOMAC Pain Score in conjunction with a minimum absolute improvement of 50 mm from baseline in the WOMAC Pain Score at four assessment points between Weeks 7/8 to 21/22 for the index knee.

1. OAK9501 Subgroup Analysis Results:

The ITT Subgroup comprised 164 patients, 83 in O3 and 81 in Saline, and was analyzed using the same analysis plan as the OAK2001 data. A significantly larger number of O3 patients had a 40% or better improvement in WOMAC Pain Score compared to Saline, as analyzed using the Generalized Estimating Equation (GEE). Similar statistically significant differences between O3 and Saline were also seen at the 50% threshold. (See Tables 3 and 4)

2. OAK2001 Subgroup Analysis Results:

In the Evaluable subgroup, a significantly larger proportion of O4 patients achieved 40% and 50% improvements from baseline in WOMAC Pain Score compared to A4 (based on GEE analysis). Three secondary endpoints (mean changes from baseline in the WOMAC Pain Score, Investigator Global Score, and Patient Global Score) were also statistically better in O4 than A4 in GEE analysis. Change from baseline in WOMAC Pain Score within treatment group was highly significant for both ORTHOVISC® groups, as well as A4. In the overall Evaluable population, two secondary endpoints (Investigator Global Score and Patient Global Score) were statistically significant by GEE analysis in the comparison of O4 vs. A4, applying the Hochberg procedure. Because A4 achieved a better than expected improvement, no statistical differences were seen between O3A1 and A4 in this study. As a result, a

combined analysis with OAK9501 was undertaken to gain additional statistical power. (See Tables 3 and 4)

3. Combined Studies Subgroup Analyses Results

In the analysis of combined data from the OAK9501 and OAK2001 studies, the effectiveness subgroup population (the ITT Subgroup from OAK9501 and the Evaluable Subgroup from OAK2001) were analyzed together, comprising 5 treatment groups (4 ORTHOVISC® injections [O4], 3 ORTHOVISC® injections followed by 1 arthrocentesis [O3A1], 3 ORTHOVISC® injections [O3], 4 arthrocentesis procedures [A4] and 3 saline injections [Saline]). For the GEE analyses, the O3A1 and O3 groups were pooled to form a sixth group [O3A1/O3] to assess superiority of the 3-injection ORTHOVISC® regimen versus Saline.

(Refer to Tables 3 and 4) A statistically significantly larger proportion of O4 patients achieved the individual patient success criteria of 40% and 50% improvements from baseline in WOMAC Pain Score coupled with a 50 mm absolute improvement compared to both A4 and Saline patients over 7-22 weeks (based on GEE analysis). The secondary endpoints: Investigator Global Score and Patient Global Score were significant in favor of O4 vs. A4 by GEE, and Pain on Standing Score, Investigator Global Score, and Patient Global Score were significant in favor of O4 vs. Saline by GEE. A significantly larger proportion of O3 patients achieved 40% and 50% improvements from baseline in WOMAC Pain Score than Saline patients (based on GEE analysis). Three secondary endpoints (Pain on Standing Score, Investigator Global Score, Patient Global Score) were significant in favor of O3A1/O3 vs. Saline by GEE.

Results of the 40% and 50% thresholds improvement from baseline in WOMAC Pain Score analyzed by gender did not reveal any significant trends on the basis of gender.

Table 3: GEE Results (P-Values) for the Effectiveness Subgroups for All Endpoints

Endpoint	O4 vs. A4	O4 vs. Saline	O3 vs. Saline	O3A1/O3 vs. Saline
20% improvement and 50 mm absolute improvement in WOMAC	NSS	NSS	NSS	NSS
40% improvement in WOMAC	0.0094	0.0015	0.0166	0.0388
50% improvement in WOMAC	0.0360	0.0015	0.0274	0.0384
Pain on standing	NSS	<0.0001	NSS	0.0206
Investigator global	0.0056	0.0002	NSS	0.0153
Patient global	0.0027	<0.0001	NSS	0.0045

NSS = Not statistically significant.

O4 4 weekly ORTHOVISC® injections--OAK2001 Study
A4 4 weekly control [arthrocentesis only] procedures--OAK2001 Study
O3 3 weekly ORTHOVISC® injections--OAK9501 Study
O3A1 3 weekly ORTHOVISC® injections + 1 control [arthrocentesis only] procedure -- OAK2001 Study
Saline 3 weekly control [saline injection] procedures--OAK9501 Study

Table 4: Summary of mean number patients achieving primary individual patient success criteria—effectiveness subgroups from OAK9501 and OAK2001—over weeks 8 through 22 (4 visits).

	O4 N = 104	O3/A1 N =90	A4 N = 100	O3 N = 83	Saline x 3 N = 81
Mean No. (%) patients achieving ≥ 20% improvement from baseline and absolute improvement of 50 mm in WOMAC Pain Score	77.5 (74.5%)	58.3 (64.7%)	64.5 (64.5%)	59.3 (71.4%)	50.8 (62.7%)
Mean No. (%) patients achieving ≥ 40% improvement from baseline in WOMAC Pain Score	68.0 (65.4%)	47.0 (52.2%)	48.8 (48.8%)	45.8 (55.1%)	34.3 (42.3%)
Mean No. (%) patients achieving ≥ 50% improvement from baseline in WOMAC Pain Score	59.3 (57.0%)	40.5 (45.0%)	43.5 (43.5%)	38.5 (46.4%)	28.3 (34.9%)

O4 4 weekly ORTHOVISC® injections--OAK2001 Study
A4 4 weekly control [arthrocentesis only] procedures--OAK2001 Study
O3 3 weekly ORTHOVISC® injections--OAK9501 Study
O3A1 3 weekly ORTHOVISC® injections + 1 control [arthrocentesis only] procedure -- OAK2001 Study
Saline 3 weekly control [saline injection] procedures--OAK9501 Study

In summary, with respect to patients achieving ≥ 40% improvement compared to baseline, the four injection ORTHOVISC® regimen demonstrated effectiveness compared to both Saline and Arthrocentesis control procedures and the three-weekly injection regimen demonstrated effectiveness over saline in the indicated patient population.

XI. CONCLUSIONS DRAWN FROM STUDIES

The effectiveness data obtained from the combined effectiveness subgroup population from two randomized studies (OAK9501 and OAK2001) provide evidence of the safety and effectiveness of ORTHOVISC® for the treatment of pain in osteoarthritis of the knee in patients who have failed to adequately respond to conservative non-pharmacological therapy and simple analgesics (e.g., acetaminophen). There were no statistically significant differences in the incidence of adverse events in the patients who received ORTHOVISC® compared to those who received each of the control treatments.

XII. PANEL RECOMMENDATION

In accordance with the provisions of section 515(c)(2) of the act in as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Orthopedic and Rehabilitation Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIII. FDA DECISION

The labeling and the safety and effectiveness data obtained from the combined effectiveness subgroup population from two randomized studies (OAK9501 and OAK2001) studies and the safety data from the OAK9801 study provide evidence to support the safety and effectiveness of ORTHOVISC® for the treatment of pain in osteoarthritis of the knee in patients who have failed to adequately respond to conservative non-pharmacological therapy and simple analgesics (e.g., acetaminophen).

XIV. APPROVAL SPECIFICATIONS

Refer to Conditions of Approval
Directions for Use: See the Labeling

Hazards to Health from use of the device: See indications, contraindications, warnings, precautions, and adverse events in the labeling.

Postapproval Requirements and Restrictions: See approval order.